

Successful Rechallenge for Oxaliplatin Hypersensitivity Reactions in Patients with Metastatic Colorectal Cancer

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Abstract. *Background: Discontinuation of oxaliplatin-containing regimens is sometimes necessary due to hypersensitivity reactions for which effective countermeasures have not yet been identified. Patients and Methods: We retrospectively reviewed cases in which hypersensitivity reactions developed in 623 patients treated with oxaliplatin for colorectal cancer. Clinical outcomes of patients who underwent oxaliplatin rechallenge with rechallenge protocol (STEP 1: hydrocortisone, chlorpheniramine, and/or ranitidine; STEP 2: hydrocortisone with an escalating dose to 500 mg, and/or prolonged administration time of oxaliplatin; and STEP 3: STEP 2 plus a subcutaneous injection of epinephrine) were examined. Results: Out of 623 patients, 126 (20.2%) patients developed hypersensitivity reactions. Out of these 126 patients, 99 (78.6%) underwent oxaliplatin rechallenge. As the initial oxaliplatin rechallenge, 19 patients received subsequent treatment without the rechallenge protocol and 80 patients received oxaliplatin with the rechallenge protocol of STEP 1 (n=64), STEP 2 (n=15), and STEP 3 (n=1). The median number of oxaliplatin rechallenges was 3 (range=1 to 29). The reason for treatment discontinuation was disease progression in 55 patients (56%) and hypersensitivity reactions in 21 patients (21%). Overall hypersensitivity reactions after rechallenge were observed in 59%, with grade 3/4 in 6%. Conclusion: The rechallenge protocol is an effective treatment option for patients with oxaliplatin hypersensitivity reactions.*

Oxaliplatin is widely used in the treatment of colorectal cancer. Oxaliplatin-containing FOLFOX therapy [i.e. oxaliplatin, 5-fluorouracil (5-FU), and leucovorin (LV)] has been demonstrated to be effective for metastatic colorectal

cancer (1-5). In the MOSAIC study of FOLFOX with 5-FU/LV as the postoperative adjuvant chemotherapy for stage III colon cancer, the efficacy of oxaliplatin addition has been demonstrated, and its use in the treatment regimen is increasing (6). The efficacy of oxaliplatin has been also demonstrated for gastric and pancreatic cancer (7-10).

Adverse reactions to oxaliplatin include nausea, vomiting, anorexia, and myelosuppression, which are usually manageable and have little effect on the continuation of oxaliplatin treatment. However, neurotoxicity and hypersensitivity reactions occasionally interfere with the continuation of oxaliplatin treatment.

Many reports on hypersensitivity reactions to platinum agents are related to cisplatin and carboplatin, and the reported incidence of reactions is 10-27% (11). According to the initial reports published after oxaliplatin was first introduced into clinical practice, the incidence of oxaliplatin-related hypersensitivity reactions was as low as 0.55% (12). However, with more frequent use, more cases of hypersensitivity reactions have been reported. Recent reports place the incidence rate at 10-25% (1.6-7.3% for events $\geq$ grade 3) (13-16). The median number of administrations until the onset of oxaliplatin-related hypersensitivity reactions is 7-9, indicating that several sensitizing exposures are necessary for the development of hypersensitivity reactions (13-17).

Oxaliplatin rechallenge for hypersensitivity reactions has been attempted using several methods such as hydrocortisone, antihistamines, epinephrine, and prolongation of oxaliplatin infusion time. However, a rechallenge protocol has not been established. Therefore, we retrospectively examined the incidence of oxaliplatin-related hypersensitivity reactions and evaluated the effectiveness of a rechallenge protocol for hypersensitivity reactions in patients with metastatic colorectal cancer treated with oxaliplatin-containing regimens.

Patients and Methods

Patients. We conducted a retrospective study of patients with colorectal cancer who had undergone rechallenge for oxaliplatin hypersensitivity reactions at the National Cancer Center Hospital,

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Tokyo between April 2005 and December 2008. Inclusion criteria for participation in this study were as follows: histologically-proven colorectal adenocarcinoma; unresectable advanced or recurrent disease; an Eastern Cooperative Oncology Group performance status (PS) of 0 or 1; adequate baseline bone marrow, hepatic, and renal function (leucocyte count $\geq 3,000/\text{mm}^3$, platelet count $\geq 100,000/\text{mm}^3$, aspartate aminotransferase and alanine aminotransferase ≤ 100 U/l, total bilirubin ≤ 1.5 mg/dl, and serum creatinine ≤ 2.0 mg/dl); and a history of more than grade 1 hypersensitivity reaction caused by oxaliplatin.

This study was approved by the Institutional Review Board of the National Cancer Center Hospital, and was conducted in compliance with the Ethical Guidelines for Epidemiological Research.

Rechallenge protocol for oxaliplatin hypersensitivity reactions. When grade 1 or 2 hypersensitivity reactions occurred, patients underwent oxaliplatin rechallenge using the following protocol in subsequent cycles. The rechallenge protocol was as follows: STEP 1: 100 mg of hydrocortisone, 10 mg of chlorpheniramine, and/or 50 mg of ranitidine were administered before the administration of oxaliplatin; STEP 2: STEP 1 plus an escalating dose of hydrocortisone for a total of 500 mg, and/or prolonged administration of oxaliplatin from the original 2 h to 6 h; and STEP 3: STEP 2 plus a subcutaneous injection of 0.3 mg (0.3 ml of 1:1000) of epinephrine with careful monitoring of cardiorespiratory signs. Patients who require STEP 3 received oxaliplatin rechallenge in the hospital for two days, and then received the rechallenge as an outpatient if its safety was confirmed.

The rechallenge protocol was conducted in a step-by-step basis for patients with serious hypersensitivity reactions, such as problems with breathing and circulatory dynamics. Physicians judged whether to terminate the oxaliplatin-containing regimen or to administer the oxaliplatin rechallenge with STEP 2 or STEP 3, and not STEP 1.

Study assessments. Hypersensitivity reactions were graded using allergic reaction/hypersensitivity of the National Cancer Institute Common Terminology Criteria for Adverse Events Version 3.0 terms (18). Allergic reaction/hypersensitivity is defined as follows: Grade 1, transient flushing or rash, and drug fever $<38^\circ\text{C}$; grade 2, rash, flushing, urticaria, dyspnea, drug fever $\geq 38^\circ\text{C}$; grade 3, symptomatic bronchospasm, with or without urticaria, parenteral medication indicated, allergy-related edema/angioedema, hypotension; and grade 4, anaphylaxis.

The following medical records for each patient were reviewed: age, sex, history of chemotherapy, treatment regimen, frequency of oxaliplatin administration and cumulative dose, onset of hypersensitivity reactions, hypersensitive symptoms and subsequent treatment, implementation/no implementation of oxaliplatin rechallenge after hypersensitivity reactions, and hypersensitivity reactions observed after oxaliplatin rechallenge.

Results

Patients' characteristics. Among 623 consecutive patients who underwent oxaliplatin-containing regimens at our hospital between April 2005 and December 2008, 126 (20.2%) developed hypersensitivity reactions. Table I shows the characteristics of patients with hypersensitivity reactions. The median number of cycles of oxaliplatin administration

Table I. *Characteristics of patients with hypersensitivity reactions (n=126).*

Category	N	%
Median age, years (range)	62 (29-83)	
Gender		
Male	67	53.2
Female	59	46.8
Chemotherapy line		
First-line	75	59.5
$\geq$ Second-line	51	40.5
Chemotherapy regimen		
FU/LV plus oxaliplatin (FOLFOX)	104	82.5
FOLFOX plus bevacizumab	16	12.7
Other*	6	4.8
Median number of cycles (range)	10 (2-31)	
Median cumulative dose of oxaliplatin mg/m^2 (range)	723 (150-2,278)	
Hypersensitivity reaction		
Grade 1	88	69.8
Grade 2	31	24.6
Grade 3	6	4.8
Grade 4	1	0.8
Oxaliplatin rechallenge		
Yes	99	78.6
No (reason for non-rechallenge)		
Progressive disease	13	10.3
Hypersensitivity reaction	9	7.1
Neurotoxicity	4	3.2
Surgery	1	0.8

Other*: FU plus oxaliplatin with concurrent radiation in 5 patients and bolus FU/LV plus oxaliplatin (FLOX) in 1 patient.

until the initial onset of hypersensitivity reaction was 10 (range=2 to 31), and the median cumulative dose was 723 mg/m^2 (range=150 to 2,278 mg/m^2).

Oxaliplatin rechallenge. Out of the 126 patients with hypersensitivity reaction, 99 (78.6%) patients underwent oxaliplatin rechallenge, while 27 patients discontinued oxaliplatin-containing treatment. Out of the 99 patients that underwent rechallenge, six patients showed deterioration in hypersensitivity reactions. For the initial oxaliplatin rechallenge, 19 patients underwent subsequent oxaliplatin treatment without the rechallenge protocol and 80 patients using the rechallenge protocol of STEP 1 (n=64), STEP 2 (n=15), and STEP 3 (n=1). Figure 1 shows the course of treatment after oxaliplatin rechallenge. The median number of oxaliplatin rechallenge administrations was three (range=1 to 29). The most frequent reason for treatment discontinuation was disease progression (55 patients, 56%), followed by hypersensitivity reactions (21 patients, 21%), neurotoxicity (13 patients, 13%) and other reasons (10 patients, 10%) (Table II and Figure 2). Of the nine patients who underwent

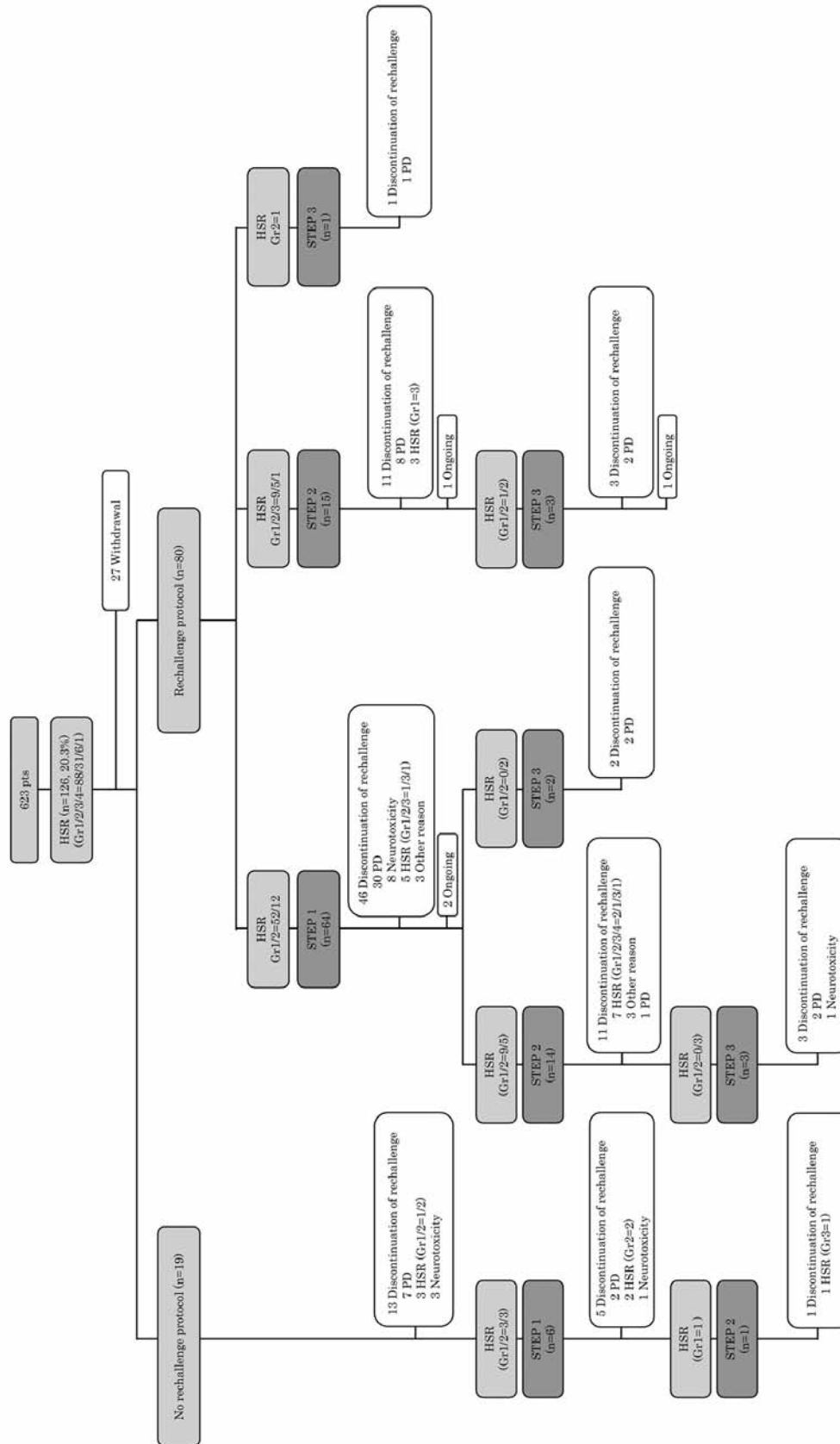


Figure 1. Flow chart of patients presenting hypersensitivity reaction to oxaliplatin. HSR, Hypersensitivity reaction; L-OHP, oxaliplatin; Gr, grade; PD, progressive disease.

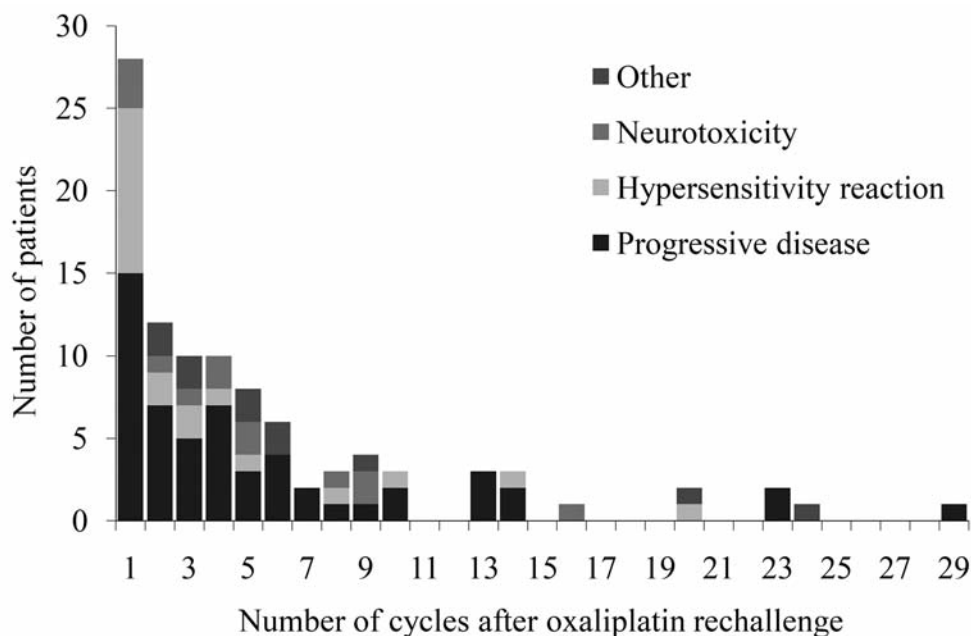


Figure 2. Number of reason for patients discontinuing treatment according to the number of treatment cycles after oxaliplatin rechallenge.

the rechallenge protocol with epinephrine (STEP 3), eight continued the oxaliplatin-containing regimen until disease progression and the remaining patient discontinued treatment due to neurotoxicity. The median number of administrations of oxaliplatin rechallenge with STEP 3 was 12 (range=1 to 29). The incidence of recurrent hypersensitivity reactions after oxaliplatin rechallenge was 59%, and 6% experienced reactions $\geq$ grade 3 (Table II).

Grade 4 hypersensitivity reaction after rechallenge occurred in one patient. This patient developed a grade 1 hypersensitivity reaction (rash and pruritus in the lower extremities) in cycle 5 of the modified FOLFOX6 (mFOLFOX6) regimen, and continued mFOLFOX6 with the rechallenge protocol at 100 mg of hydrocortisone and 10 mg of chlorpheniramine (STEP 1) in subsequent cycles. After 15 cycles of mFOLFOX6, a grade 1 hypersensitivity reaction (same rash) occurred again. Hydrocortisone administration was increased to 300 mg (STEP 2). In cycle 23 of mFOLFOX6, a grade 4 hypersensitivity reaction (nausea, dyspnea accompanied by a fall in percutaneous oxygen saturation 86%, and a severe drop in blood pressure to 85/42 mmHg) developed. Subsequent mFOLFOX6 was discontinued.

Discussion

The 20.2% (126/623 patients) incidence of oxaliplatin-related hypersensitivity reactions in our study is comparable to the incidence (10-25%) reported previously (13-16). Our

Table II. Outcome of oxaliplatin rechallenge (n=99).

	N
Median number of oxaliplatin rechallenge (range)	3 (1-29)
Reason for treatment discontinuation	
Progressive disease	55
Hypersensitivity reaction	21
Neurotoxicity	13
Other	10
Worst grade of hypersensitivity reaction	
Grade 0	41
Grade 1	29
Grade 2	23
Grade 3	5
Grade 4	1

study revealed that 55 (56%) out of 99 patients who underwent oxaliplatin rechallenge were able to tolerate oxaliplatin in the rechallenge protocol until disease progression, although the median number of oxaliplatin rechallenges was three (range=1-29).

When the symptoms of oxaliplatin-related hypersensitivity reactions were mild, oxaliplatin rechallenge was frequently attempted. One such measure is the administration of steroids and anti-histamines prior to oxaliplatin rechallenge. According to a report by Siu *et al.*, out of 27 patients with

hypersensitivity reactions, 14 patients with grade 1 or 2 hypersensitivity reactions were pre-medicated with steroids and anti-histamines before oxaliplatin rechallenge, and four (28.6%) developed a recurrence of hypersensitivity reactions. Two of these patients (14.3%) exhibited a grade 3 or 4 hypersensitivity reaction (14). Syrigou *et al.* reported that 32 out of 48 patients with grade 1 or 2 hypersensitivity reactions were pre-medicated with steroids/antihistamines, and hypersensitivity reactions recurred in 20 (62.5%) patients after the oxaliplatin rechallenge (19). Since concurrent therapy with steroids and anti-histamines did not completely inhibit the recurrence of hypersensitivity reactions, precautions are needed in the case of oxaliplatin rechallenge. Furthermore, Rakkar *et al.* reported that the subcutaneous administration of epinephrine was effective for oxaliplatin rechallenge. According to this report, when epinephrine (0.3 ml, 1:1000 solution) was administered prophylactically, together with the usual pre-medications of steroids and anti-histamines in five patients who developed oxaliplatin-related hypersensitivity reactions, no hypersensitivity reaction recurred, and a maximum of 14 cycles of oxaliplatin-containing regimen was possible (20).

In addition to these reports on pre-medications, a rechallenge protocol of prolongation of oxaliplatin infusion time for prophylaxis has been reported. According to Maindault-Goebel *et al.*, the duration of oxaliplatin administration for rechallenge was extended from 2 to 6 h in five patients who had developed laryngospasm in reaction to oxaliplatin, and no recurrence of the symptom was observed (14). Although the mechanism of inhibition of hypersensitivity reactions by prolongation of the infusion time is not known, it is possible that the maximum blood concentration levels are reduced with prolongation of oxaliplatin infusion time.

From the results of our study, we recommend the following treatment for oxaliplatin-related hypersensitivity reactions. If grade 1 or 2 hypersensitivity reactions (excluding dyspnea) occur, patients should continue oxaliplatin-containing treatment with the rechallenge protocol. However, when grade 2 or 3 hypersensitivity reactions occur, such as cardiovascular or respiratory symptoms, the decision to continue or terminate oxaliplatin-containing treatment should be made carefully. If subsequent chemotherapies, such as irinotecan or anti-epidermal growth factor receptor antibodies are active, we recommend their use or use of continuous infusion of 5-FU/LV without oxaliplatin. Then, if all key drugs have been administered to completion, oxaliplatin-containing treatment should be selected with the rechallenge protocol of STEP 2 or STEP 3 after informed consent is provided by the patient, who must be made aware of the risk of life-threatening complications (21). If consent is not provided, patients with serious hypersensitivity reactions should receive the best supportive care or participate in a clinical trial.

In conclusion, the rechallenge protocol was effective in patients with oxaliplatin hypersensitivity reactions. The rechallenge protocol should be selected as a treatment option according to the remaining available key agents for colorectal cancer.

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Conflicts of Interest

The Authors have no potential conflicts of interest to declare.

References

- 1 de Gramont A, Figuer A, Seymour M, Homerin M, Hmissi A, Cassidy J, Boni C, Cortes-Funes H, Cervantes A, Freyer G, Papamichael D, Le Bail N, Louvet C, Hendler D, de Braud F, Wilson C, Morvan F and Bonetti A: Leucovorin and fluorouracil with or without oxaliplatin as first-line treatment in advanced colorectal cancer. *J Clin Oncol* 18: 2938-2947, 2000.
- 2 Goldberg RM, Sargent DJ, Morton RF, Fuchs CS, Ramanathan RK, Williamson SK, Findlay BP, Pitot HC and Alberts SR: A randomized controlled trial of fluorouracil plus leucovorin, irinotecan, and oxaliplatin combinations in patients with previously untreated metastatic colorectal cancer. *J Clin Oncol* 22: 23-30, 2004.
- 3 Saltz LB, Clarke S, Díaz-Rubio E, Scheithauer W, Figuer A, Wong R, Koski S, Lichinitser M, Yang TS, Rivera F, Couture F, Sirzén F and Cassidy J: Bevacizumab in combination with oxaliplatin-based chemotherapy as first-line therapy in metastatic colorectal cancer: A randomized phase III study. *J Clin Oncol* 26: 2013-2019, 2008.
- 4 Tournigand C, André T, Achille E, Lledo G, Flesh M, Mery-Mignard D, Quinaux E, Couteau C, Buyse M, Ganem G, Landi B, Colin P, Louvet C and de Gramont A: FOLFIRI followed by FOLFOX6 or the reverse sequence in advanced colorectal cancer: A randomized GERCOR study. *J Clin Oncol* 22: 229-237, 2004.
- 5 Rothenberg ML, Oza AM, Bigelow RH, Berlin JD, Marshall JL, Ramanathan RK, Hart LL, Gupta S, Garay CA, Burger BG, Le Bail N and Haller DG: Superiority of oxaliplatin and fluorouracil-leucovorin compared with either therapy alone in patients with progressive colorectal cancer after irinotecan and fluorouracil-leucovorin: interim results of a phase III trial. *J Clin Oncol* 21: 2059-2069, 2003.
- 6 André T, Boni C, Mounedji-Boudiaf L, Navarro M, Tabernero J, Hickish T, Topham C, Zaninelli M, Clingan P, Bridgewater J, Tabah-Fisch I and de Gramont A: Multicenter International Study of Oxaliplatin/5-Fluorouracil/Leucovorin in the Adjuvant Treatment of Colon Cancer (MOSAIC) Investigators: Oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment for colon cancer. *N Engl J Med* 350: 2343-2351, 2004.
- 7 Cunningham D, Starling N, Rao S, Iveson T, Nicolson M, Coxon F, Middleton G, Daniel F, Oates J and Norman AR; Upper Gastrointestinal Clinical Studies Group of the National Cancer Research Institute of the United Kingdom: Capecitabine and oxaliplatin for advanced esophagogastric cancer. *N Engl J Med* 358: 36-46, 2008.

- 8 Al-Batran SE, Hartmann JT, Probst S, Schmalenberg H, Hollerbach S, Hofheinz R, Rethwisch V, Seipelt G, Homann N, Wilhelm G, Schuch G, Stoecklacher J, Derigs HG, Hegewisch-Becker S, Grossmann J, Pauligk C, Atmaca A, Bokemeyer C, Knuth A and Jäger E: Arbeitsgemeinschaft Internistische Onkologie: Phase III trial in metastatic gastroesophageal adenocarcinoma with fluorouracil, leucovorin plus either oxaliplatin or cisplatin: A study of the Arbeitsgemeinschaft Onkologie. *J Clin Oncol* 26: 1435-1442, 2008.
- 9 Pelzer U, Schwaner I, Stieler J, Adler M, Seraphin J, Dörken B, Riess H and Oettle H: Best supportive care (BSC) *versus* oxaliplatin, folinic acid and 5-fluorouracil (OFF) plus BSC in patients for second-line advanced pancreatic cancer: A phase III study from the German CONKO-study group. *Eur J Cancer* 47: 1676-1681, 2011.
- 10 Conroy T, Desseigne F, Ychou M, Bouché O, Guimbaud R, Bécouarn Y, Adenis A, Raoul JL, Gourgou-Bourgade S, de la Fouchardière C, Bennouna J, Bachet JB, Khemissa-Akouz F, Péré-Vergé D, Delbaldo C, Assenat E, Chauffert B, Michel P, Montoto-Grillot C and Ducreux M; Groupe Tumeurs Digestives of Unicancer; PRODIGE Intergroup: FOLFIRINOX *versus* gemcitabine for metastatic pancreatic cancer. *N Engl J Med* 364: 1817-1825, 2011.
- 11 Shepherd GM: Hypersensitivity reactions to chemotherapeutic drugs. *Clin Rev Allergy Immunol* 24: 253-262, 2003.
- 12 Thomas RR, Quinn MG, Schuler B and Grem JL: Hypersensitivity and idiosyncratic reactions to oxaliplatin. *Cancer* 97: 2301-2307, 2003.
- 13 Brandi G, Pantaleo MA, Galli C, Falcone A, Antonuzzo A, Mordenti P, Di Marco MC and Biasco G: Hypersensitivity reactions related to oxaliplatin (OHP). *Br J Cancer* 89: 477-481, 2003.
- 14 Siu SW, Chan RT and Au GK: Hypersensitivity reactions to oxaliplatin: Experience in a single institute. *Ann Oncol* 17: 259-261, 2006.
- 15 Polyzos A, Tsavaris N, Kosmas C, Gogas H, Toufexi H, Kosmidis C, Markopoulos C, Giannopoulos A, Papadopoulos O, Stamatiadis D and Kouraklis G: Clinical features of hypersensitivity reactions to oxaliplatin: A 10-year experience. *Oncology* 76: 36-41, 2009.
- 16 Kim BH, Bradley T, Tai J and Budman DR: Hypersensitivity to oxaliplatin: An investigation of incidence and risk factors, and literature review. *Oncology* 76: 231-238, 2009.
- 17 Maindault-Goebel F, André T, Tournigand C, Louvet C, Perez-Staub N, Zeghib N and De Gramont A: Allergic-type reactions to oxaliplatin: Retrospective analysis of 42 patients. *Eur J Cancer* 41: 2262-2267, 2005.
- 18 Cancer Therapy Evaluation Program, Common Terminology Criteria for Adverse Events, Version 3.0, DCTD, NCI, NIH, DHHS March 31, 2003. Available at: <http://ctep.cancer.gov>. Publish Date: August 9, 2006.
- 19 Syrigou EI, Karapanagiotou EM, Alamara CV, Boura PG, Saif MW and Syrigos KN: Hypersensitivity reactions to oxaliplatin: A retrospective study and the development of a desensitization protocol. *Clinical Colorectal Cancer* 8: 106-109, 2009.
- 20 Rakkar AS: Management of hypersensitivity reactions to oxaliplatin with SC epinephrine. *Gastrointestinal Cancers Symposium abstract* 258, 2006.
- 21 Iwasa S, Hamaguchi T, Tada K, Yanai T, Hashimoto H, Nakajima TE, Kato K, Yamada Y and Shimada Y: Prophylactic administration of epinephrine in oxaliplatin-related hypersensitivity reaction. *J Clin Oncol* 29(suppl 4): abstr 610, 2011.

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